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Variant: NM_003159.3:c.2714-3909A>T

Version: 1.0

CA412370385

Gene: CDKL5 (HGNC:6792)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: fd0cb767-3414-4096-af71-5e2d152b6437
Approved on: 2025/9/23
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HGVS expressions

NM_003159.3:c.2714-3909A>T
NC_000023.11:g.18642098A>T
CM000685.2:g.18642098A>T
NC_000023.10:g.18660218A>T
CM000685.1:g.18660218A>T
NC_000023.9:g.18570139A>T
NG_008475.1:g.221494A>T
NG_008659.3:g.40351T>A
ENST00000379984.4:c.581T>A
ENST00000379984.3:c.581T>A
ENST00000379989.6:c.2714-3909A>T
ENST00000379996.7:c.2714-3909A>T
ENST00000476595.1:n.1072T>A
NM_000330.3:c.581T>A
NM_001037343.1:c.2714-3909A>T
NM_003159.2:c.2714-3909A>T
NM_000330.4:c.581T>A
NM_001037343.2:c.2714-3909A>T

Pathogenic

Met criteria codes 5

PP4_Moderate PP1_Strong PP3_Strong PM2_Supporting PS4_Supporting

Evidence Links 0

Expert Panel

X-linked Inherited Retinal Disease VCEP

Criteria Specification Information

Criteria Specification: *ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

X-linked Inherited Retinal Disease VCEP

NM_000330.4(RS1):c.581T>A (p.Ile194Asn) is a missense variant encoding the substitution of isoleucine with asparagine at position 194. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 29739629, PMID: 19324861, PS4_Supporting). At least one proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years, and showing retinal detachment, which together are highly specific for X-linked retinoschisis (PMID: 32300273, PP4_Moderate). The variant has been reported to segregate with affected status through 3 meioses within 1 family (PP1_Strong; PMID: 24505212). The computational predictor REVEL gives a score of 0.956, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_Strong). The computational splicing predictor SpliceAI gives a delta score of 0.00 for all predictive splice changes, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing. In summary, this variant is classified as pathogenic for X-linked retinoschisis based on the ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0: PM2_Supporting, PP3_Strong, PP1_Strong, PP4_Moderate, and PS4_Supporting.

Met criteria codes

PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years, and showing retinal detachment, which together are highly specific for X-linked retinoschisis (PMID: 32300273, PP4_Moderate).
PP1_Strong	✔	The variant has been reported to segregate with affected status through 3 meioses within 1 family (PP1_Strong; PMID: 24505212).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.956, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_Strong). The computational splicing predictor SpliceAI gives a delta score of 0.00 for all predictive splice changes, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing.
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting	✔	This variant has been reported in at least 2 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 29739629, PMID: 19324861, PS4_Supporting).

Curation History

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